Claims

1. An isolated recombinant nucleic acid compound that comprises a nucleotide sequence encoding at least a domain of an epothilone polyketide synthase (PKS) protein and/or encoding a functional region of an epothilone modification enzyme.

2. The nucleic acid of claim 1, wherein said domain is selected from the group consisting of a loading domain, a thioesterase domain, an NRPS, an AT domain, a KS domain, an ACP domain, a KR domain, a DH domain, and an ER domain, a methyl transferase domain and a functional oxidase domain.

3. The nucleic acid of claim 1 or 2 that comprises the coding sequence of an *epoA* gene, and/or

the coding sequence of an *epoB* gene, and/or

the coding sequence of an *epoC* gene, and/or

the coding sequence of an *epoD* gene, and/or

the coding sequence of an *epoE* gene, and/or

the coding sequence of an *epoF* gene, and/or

the coding sequence of an *epoK* gene, and/or

the coding sequence of an *epoL* gene.

4. The nucleic acid of any of claims 1-3 that further comprises a promoter positioned to transcribe said encoding nucleotide sequence in host cells in which said promoter is operable.

5. The nucleic acid of claim 4, wherein said promoter is a promoter from a *Sorangium* gene, or

from a *Myxococcus* gene, or

from a *Streptomyces* gene, or

from an epothilone PKS gene, or

from a *pilA* gene, or

from an actinorhodin PKS gene.

6. The nucleic acid of any of claims 1-5 that is a recombinant DNA expression vector.

7. Host cells which contain the nucleic acid of any of claims 4-6.

8. The cells of claim 7 which are *Sorangium* cells, or

Myxococcus cells, or

Pseudomonas cells, or

Streptomyces cells.

9. A method to produce a polyketide which method comprises culturing the cells of claim 7 or 8 under conditions wherein the encoding nucleotide sequence is expressed to obtain a functional PKS.

10. A recombinant *Sorangium cellulosum* host cell that contains a mutated gene for an epothilone PKS protein or epothilone modification enzyme, wherein said mutated gene was inserted in whole or in part into genomic DNA of said cell by homologous recombination with a recombinant vector comprising all or a part of an epothilone PKS gene or epothilone modification gene.

11. The recombinant host cell of claim 10 that

makes epothilone C or D but not A or B due to a mutation inactivating or deleting an *epoK* gene, or

makes epothilone A or C but not B or D due to a mutation in *epoD* altering module 4 AT domain specificity, or

makes epothilone B or D but not A or C due to a mutation in *epoD* altering module 4 AT domain specificity, or

makes epothilone C but not epothilone A, B or D due to a mutation in *epoD* altering module 4 AT domain specificity and a mutation in *epoK*, or

makes epothilone D but not epothilone A, B or C due to a mutation in *epoD* altering module 4 AT domain specificity and a mutation in *epoK*.

12. Recombinant *Streptomyces* or *Myxococcus* host cells that express an epothilone PKS gene or an epothilone modification enzyme gene, optionally comprising one or more of said epothilone PKS or modification enzyme genes integrated into their chromosomal DNA and/or one or more of said epothilone PKS or modification enzyme genes on an extrachromosomal expression vector.

13. The host cells of claim 12 or 13 that are *S. coelicolor* CH999.

14. A method to produce an epothilone or epothilone derivative which comprises culturing the cells of claims 12 or 13.

15. A modified functional epothilone PKS wherein said modification comprises at least one of:

replacement of at least one AT domain with an AT domain of different specificity;

inactivation of the NRPS-like module 1 or of the KS2 catalytic domain;

inactivation of at least one activity in at least one β-carbonyl modification domain;

addition of at least one of KR, DH and ER activity in at least one β-carbonyl modification domain; and

replacement of the NRPS module 1 with an NRPS of different specificity.

16. The modified PKS of claim 15 contained in a cell or contained in a cell-free system, wherein said cell or system contains additional enzymes for modification of the product of said epothilone PKS.

17. The modified PKS of claim 16 wherein said modifying enzymes comprise at least one of a methyltransferase, an oxidase or a glycosylation enzyme.

18. A method to prepare an epothilone derivative which method comprises providing substrates including extender units to the modified PKS of any of claims 15-17.

19. A modified functional epothilone PKS wherein said modification comprises inactivation of the NRPS of module 1 or the KS2 of module 2 thereof.

20. A method to make an epothilone derivative which method comprises contacting the modified PKS of claim 19 with a module 2 substrate or a module 3 substrate and extender units.

21. Recombinant host cells which comprise the modified PKS of any of claims 15-17 or 19.

22. The cells of claim 21 that produce an epothilone derivative selected from the group consisting of 16-desmethyl epothilones, 14-methyl epothilones, 11-hydroxyl epothilones, 10-methyl epothilones, 8,9-anhydro epothilones, 9-hydroxyl epothilones, 9-keto epothilones, 8-desmethyl epothilones, and 6-desmethyl epothilones.

23. A compound selected from the group consisting of 16-desmethyl epothilones, 14-methyl epothilones, 11-hydroxyl epothilones, 10-methyl epothilones, 8,9-anhydro epothilones, 9-hydroxyl epothilones, 9-keto epothilones, 8-desmethyl epothilones, and 6-desmethyl epothilones.

24. A recombinant PKS enzyme that comprises one or more domains, modules, or proteins of a non-epothilone PKS and one or more domains, modules, or proteins of an epothilone PKS, and/or

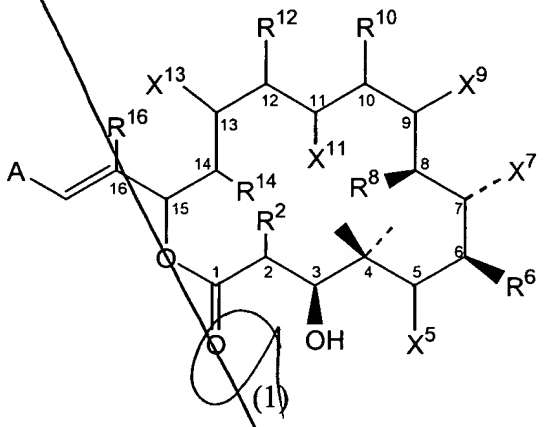
contains a loading domain that comprises a KS^Q domain.

25. The PKS enzyme of claim 24, wherein

said PKS comprises a DEBS loading domain and 5 modules of DEBS and an NRPS of the epothilone PKS,

wherein said PKS comprises all of a non-epothilone PKS with an MT domain of the epothilone PKS.

26. A compound of the formula:



including the glycosylated forms thereof and stereoisomeric forms where the stereochemistry is not shown,

wherein A is a substituted or unsubstituted straight, branched chain or cyclic alkyl, alkenyl or alkynyl residue optionally containing 1-3 heteroatoms selected from O, S and N; or wherein A comprises a substituted or unsubstituted aromatic residue;

R^2 represents H,H, or H,lower alkyl, or lower alkyl,lower alkyl;

X^5 represents =O or a derivative thereof, or H,OH or H,NR_2 wherein R is H, alkyl or acyl, or $H,OCOR_2$, $H,OCONR_2$ wherein R is H or alkyl, or is H,H;

R^6 represents H or lower alkyl, and the remaining substituent on the corresponding carbon is H;

X^7 represents OR, or NR_2, wherein R is H, alkyl or acyl or is OCOR, or $OCONR_2$ wherein R is H or alkyl or X^7 taken together with X^9 forms a carbonate or carbamate cycle, and wherein the remaining substituent on the corresponding carbon is H;

R^8 represents H or lower alkyl and the remaining substituent on the carbon is H;

X^9 represents =O or a derivative thereof, or H,OR or H,NR_2 wherein R is H, alkyl or acyl, or is H,OCOR or $H,OCONR_2$, wherein R is H or alkyl, or represents H,H or wherein X^9 together with X^7 or with X^{11} can form a cyclic carbonate or carbamate;

R^{10} is H,H or H,lower alkyl, or lower alkyl,lower alkyl;

X^{11} is =O or a derivative thereof, or H,OR, or H,NR_2 wherein R is H, alkyl or acyl or H,OCOR or $H,OCONR_2$ wherein R is H or alkyl, or is H,H or wherein X^{11} in combination with X^9 may form a cyclic carbonate or carbamate;

R^{12} is H,H, or H,lower alkyl, or lower alkyl,lower alkyl;

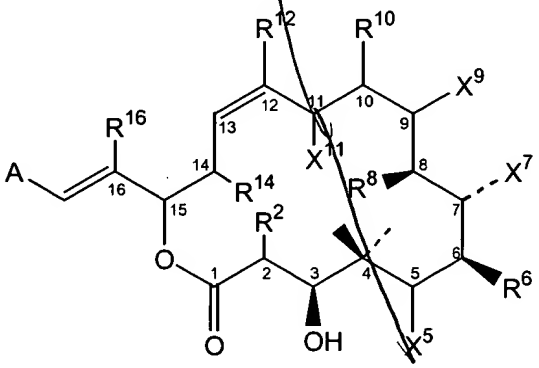
X^{13} is =O or a derivative thereof, or H,OR or H,NR_2 wherein R is H, alkyl or acyl or is H,OCOR or $H,OCONR_2$ wherein R is H or alkyl;

R^{14} is H,H, or H,lower alkyl, or lower alkyl,lower alkyl;

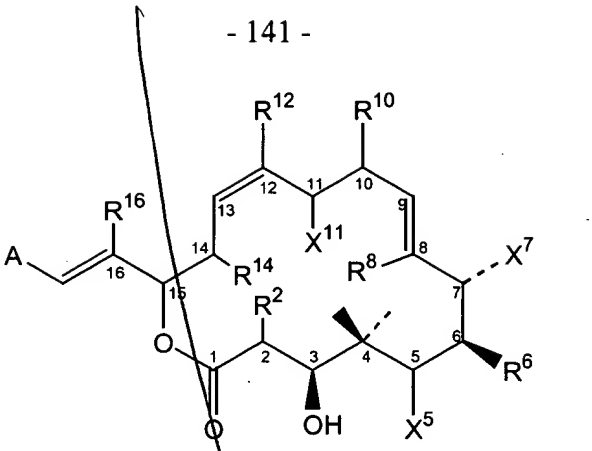
R^{16} is H or lower alkyl; and

wherein optionally H or another substituent may be removed from positions 12 and 13 and/or 8 and 9 to form a double bond, wherein said double bond may optionally be converted to an epoxide.

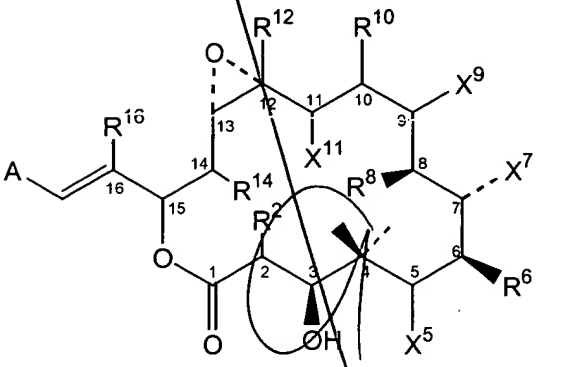
27. A compound of the formula



1(a),



1(b),



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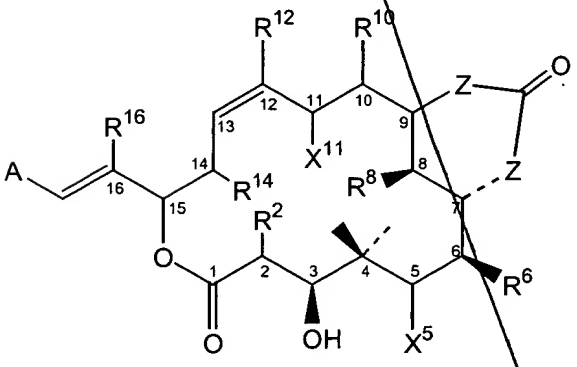
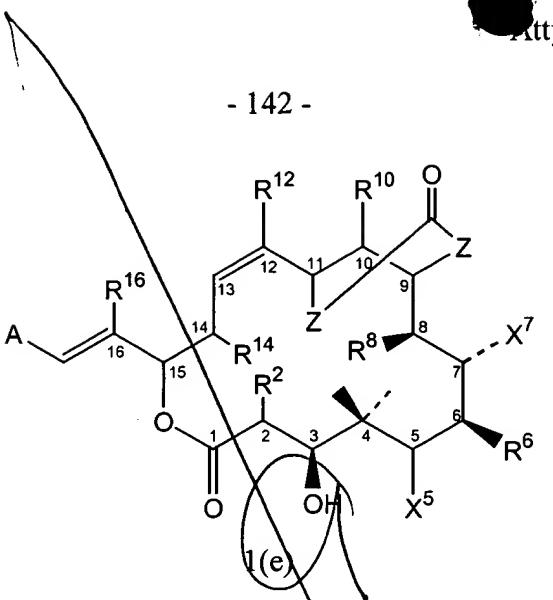


1(d),

and



wherein both Z are O or one Z is N and the other Z is O and the remaining substituents are defined as in claim 26.

28. A recombinant vector selected from the group consisting of pKOS35-70.8A3, pKOS35-70.1A2, pKOS35-70.4, pKOS35-79.85, pKOS039-124R, and pKOS039-126R.